Letters to the Editor . . .

CANCER AND THE EMBRYONAL HYPOTHESIS

One of the oldest and yet most persistent theories of cancer genesis is the embryonal one. As early as 1829 Lobstein and Recamier compared the growth of tumors to that of embryonal tissue. In 1854 the embryologist Robert Remak first proposed the theory that cancer as well as certain benign tumors arose from groups of misplaced somatic cells comprising embryonic "rests" or residues. Some years later Julius Cohnheim adopted the theory, and largely through his influence it gained wide and lasting currency. Historically, then, the "Cohnheim theory" is more accurately described as the "Remak-Cohnheim theory."

The theory of embryonic rests came as a logical consequence of the universal acceptance of Kaspar Friedrich Wolff's thesis of epigenesis, which completely supplanted the preformationist theories of the ovulists and homunculists. The proponents of epigenesis reasoned that if embryogenesis does not involve the unfolding and expansion of a preformed organism, then the development of an organism from the egg must involve the gradual adding of part-to-part much in the same manner that a house is assembled from a mass of bricks. What is more natural, they reasoned, than that some of these "bricks" be misplaced in the process of building?

The mechanistic aspect of this literal interpretation of epigenesis became apparent when examined in the light of Hans Spemann's researches, published in 1900, on organizer action and embryonic induction. Spemann showed that the surface ectoderm of *any* part of the early embryo when placed over the optic vesicle underwent lens induction. Others have since been able to duplicate this induction phenomenon through the use of a number of various chemicals.

Experiments of the nature of Spemann's have since been multiplied an hundredfold. Data from thousands of other transplantations in experimental embryology may be summarized as follows: (1) when a piece of embryonic tissue that has not yet been determined or differentiated into a specific organ type is transplanted into another organ field, the transplant differentiates in conformity with the morphological pattern of the host organ; (2) when a piece of embryonic tissue is transplanted after determination, it differentiates at the transplanted site in conformity with the morphological pattern of the site from which it was derived. Since any hypothetical misplacement of embryonic cells would necessarily occur very early in development, such cells would differentiate according to the tissue in which they were misplaced; hence they could form no so-called embryonic rests.

Oberling has summarized the case against the embryonal hypothesis of carcinogenesis very well: "It is true that embryonal cells do somewhat resemble cancer cells in appearance, but the two are entirely different in nature. For whereas the proliferative vigor of the former gradually flags as they differentiate to form normal tissues, their malignant prototypes continue to multiply indefinitely and end at last in anarchy and ruin.

"But, it may be said, in the embryo growth is restricted by controlling and directing influence; in the body of the adult, where these are missing, the embryonal cells behave quite differently. Experiment does not confirm this objection. Embryonal tissues in all stages of development have been inoculated into countless adult animals, and always with the same outcome; they never changed their character, but continued to act as they do in the embryo, growing for a time but ending as mature tissue."

Although the cancer cell is not embryonic, neither is it a spontaneously created component of the life-cycle. As Virchow pointed out long ago, no morbid process can evoke from a cell or cells potentialities that are not inherent. The cancer cell has its normal counterpart in the animal life-cycle, and this counterpart is the *non-embryonic* trophoblast cell of the early conceptus. The trophoblast cells develop before the definitive embryo, form no part of the definitive embryo, and may persist after the embryo is gone. The trophoblast cells arise as a result of the initial cleavage of a gametogenous cell that in turn has arisen from the meiosis of a diploid totipotent cell. Although inadequacies in earlier terminology have obscured the fact, *the trophoblast cell is the very antithesis of the embryonic cell,* and will destroy definitive embryonic cells in a malignant fashion when cultured with them *in vitro.* The malignancy of the normal trophoblast cell, removed from the checking influence of the mother, is not exceeded by any known exhibition of cancer.

While the facts of modern embryology dispose of the embryonic theory of cancer by disposing of embryonic rests, modern embryology recognizes the migration of specific non-embryonic cells during embryonic development: these cells are the diploid totipotent cells that comprise the morphologically continuous line of germ-cells that extend from generation to generation. A great number of workers have proved the migration and ectopic dispersion of these cells in animals and in man. The diploid totipotent cells that enter the normal canalization of the gonads must undergo meiosis to produce functional gametes. The division of a gametogenous cell so produced can occur only by the initial production of trophoblast, which marks the earliest stage of the conceptus. If the production of trophoblast occurs through the meiosis of an ectopic totipotent cell, the resulting trophoblast is either destroyed or exhibited as cancer—the most malignant exhibition of which consists of the frank trophoblast cells of extra-genital chorionepithelioma. As we have frequently emphasized, a tropho-

blast cell has *never* been observed in the male except as the most malignant exhibition of cancer—nor so in the female outside of the canalization of pregnancy.

There is no known property of the cancer cell which is not possessed by the trophoblast cell. Trophoblast cells in every respect indistinguishable from those of normal pregnancy comprise the most malignant exhibition of cancer: chorionepithelioma. Primary chorionepitheliomas have been found extra-genitally in both sexes (thus again proving the ectopic presence of the parent totipotent cell), and some of the trophoblast cells comprising these tumors have been exhibited as adenocarcinoma or sarcoma in metastases. In examining over 900 cases of testicular tumors, Friedman and Moore found the majority of them to contain frank cellular and syncytial trophoblast. In some cases the trophoblast was overt only in metastases, in other cases only at the primary site, and in many cases in both sites.

Like many other ideas in science that have been favorably received over several generations, the thesis of the so-called embryonic nature of cancer and the idea of embryonal rests are thus not entirely without justification. The so-called lost cells are the totipotent migrating germ-cells and the so-called embryonal cells are the trophoblast cells. This parallelism, however, cannot mitigate the urgency for the strictest precision in our terminology on the subject of growth and development.

Although it is not possible to attempt here an outline of the evidence for the trophoblastic nature of cancer, this is the only thesis of carcinogenesis for which not a single tenable theoretical or experimental contradiction has ever been found. A wealth of positive data exists for the support of the trophoblast thesis.

It is true that somatic cells and tissues are sometimes found in anomalous positions, but this is the result of anomalous organizer action on highly competent or undifferentiated cells—and not the result of their mechanical transposition. Just as the osseous tissue that sometimes can be induced in skin by the prolonged application of methylchloranthine is due, not to mechanically displaced bone cells but to the anomalous organizer effect exerted by the chemical on highly competent cells, so the whole phenomenon of carcinogenesis — according to the trophoblast thesis—has as its basis organizer phenomena which involve exclusively the meiosis of a totipotent cell with the consequent evocation of the pleomorphic trophoblast cells that (however masked morphologically by the tissue field in which they find themselves) form the constant malignant component of all exhibitions of cancer.

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REHABILITATION OF TUBERCULOUS PATIENTS

I note a very liberal quotation in CALIFORNIA MEDICINE, November, 1946, issue; Vol. 65, No. 5, page 58, quoting from the current issue of *Hygeia* on "Rehabilitation of Tuberculous Patients" by Joseph B. Rosner, M.D., of the National Jewish Hospital, Denver, Colorado.

I should like to take exception to point No. 5 in this program. As far as the patient is concerned, this is really the key point in all of those that are mentioned. I am quite sure that it is not current opinion among experienced phthisiologists that "it is not wise for a patient to return to the occupation in which he was engaged before becoming ill." I believe, in general, that the advice given is exactly the reverse of this, unless the occupation is definitely unsuitable—which holds true for persons doing heavy manual labor or those exposed to a silica hazard. I know the general composition of the patients in the National Jewish Hospital in Denver, and I am sure this is not good advice for them.

This point, I feel, is very important. Many patients, as well as a number of doctors, will undoubtedly read this article, and may be influenced by it. *Hygeia* is generally a very reliable publication. I believe that some step should be taken to confirm my opinion, and a definite effort made to counteract the unfavorable advice which will be given, I am afraid, to many patients on the basis of this statement.

Sincerely yours,

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